

HEMSLEYANIDINE AND ISOHEMSLEYANIDINE FROM *ACONITUM HEMSLEYANUM* VAR. *CIRCINATUM*

Qing-Yan Xu,^{a)} Zheng-Ban Li,^{a)} Feng-Peng Wang,^{a)*} and Chun-Tao Che^{b)*}

^{a)} Department of Chemistry of Medicinal Natural Products, School of Pharmacy, West China University of Medical Sciences, Chengdu, China

^{b)} Department of Chemistry, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong

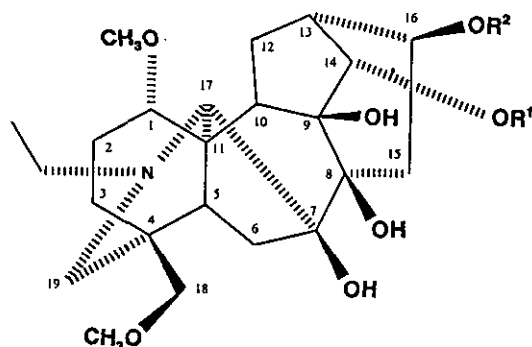
Abstract - Two new norditerpenoid alkaloids, hemsleyanidine (1) and isohemsleyanidine (2), have been isolated from the roots of *Aconitum hemsleyanum* var. *circinatum*, along with a known compound talatizamine. The structures of the new compounds were established by chemical and spectroscopic methods (including ¹H-, ¹³C-, and 2-D nmr techniques).

INTRODUCTION

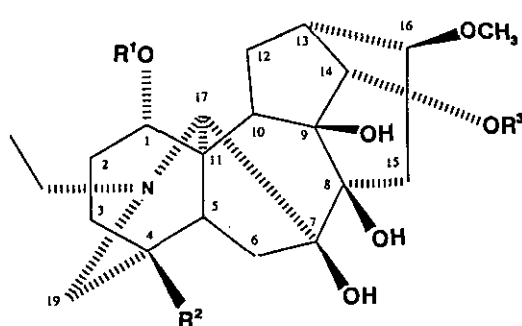
Plants belonging to the genus *Aconitum* are rich sources of diterpenoid alkaloids.¹ As part of a study on the diterpenoid alkaloid constituents of *Aconitum* and *Delphinium* species in China, we have isolated a number of norditerpenoid alkaloids from these plants, including new compounds crassicaudine,² crassicausine,² crassicautine,² gyalanines A and B,³ potanidines A and B,⁴ potanine,⁵ potanisines A-E, as well as known compounds such as lycotonine, anthranoyllycotonine, methyllycaconitine, delsemines A and B, delavaines A and B, and takaosamine. Further studies have now led to the isolation of two new norditerpenoid alkaloids, hemsleyanidine (1) and isohemsleyanidine (2), together with a known compound talatizamine,⁶ from the roots of *Aconitum hemsleyanum* Pritz. var. *circinatum* W. T. Wang (Ranunculaceae). In Chinese folk medicine, the root part of this plant is used for the treatment of rheumatism and neuralgia. A literature search indicated that yunnaconitine has been reported from this plant.⁷ The present paper deals with the isolation and structure determination of the new constituents (1 and 2).

RESULTS AND DISCUSSION

Hemsleyanidine (1) was isolated as an amorphous powder, [α]_D -8.9° (CHCl₃, c 0.71). The compound was assigned to the molecular formula C₃₁H₄₃NO₉ by CI-ms (*m/z* 574 [M + 1]⁺) in combination with hydrogen and carbon counts in the nmr spectra. Its ir spectrum showed absorption bands for OH groups



- 1 $R^1 = H; R^2 = As$
 2 $R^1 = As; R^2 = H$
 4 $R^1 = Ac; R^2 = As$
 5 $R^1 = As; R^2 = Ac$
 7 $R^1 = R^2 = H$
 8 $R^1 = R^2 = Ac$
 9 $R^1 = H; R^2 = Ac$



- 3 $R^1 = R^3 = CH_3$
 $R^2 = -O_2C-C_6H_4-NH_2(o)$
 6 $R^1 = R^3 = H$
 $R^2 = CH_3$

 $As = -CO-C_6H_4-OCH_3(p)$
 $Ac = -CO-CH_3$

(3350 cm^{-1}). The 1H - and ^{13}C -nmr spectra indicated the presence of two OCH_3 groups (δ_H 3.27, 3.31; δ_C 56.3, 59.4), an anisoyl ester [δ_H 3.82 (3H, *s*), 6.88 and 8.01 (each 2H, AA'BB' system); δ_C see Table 1], and an *N*-ethyl group [δ_H 1.11 (3H, *t*, $J = 7$ Hz); δ_C 13.3 *q*, 49.0 *t*]. Along with the above-mentioned signals, the ^{13}C -nmr spectrum displayed 19 carbon signals, nine of which (δ 60 - 85) can be attributed to oxygenated or nitrogenated carbons. The spectral characteristics of compound (1) are indicative of a norditerpenoid alkaloidal structure, and the compound was considered to be a lycocotonine-type by comparison of the nmr properties with known compounds such as ranaconitine.⁸

One of the OCH_3 groups (δ_C 59.4) was readily assigned to locate at C-18 because the latter carbon was apparently oxygenated (δ 78.4). Typically, C-18 bearing an OCH_3 resonates at around δ 78 in many norditerpenoid alkaloids.¹ Further examination of the $^1H, ^1H$ -COSY and $^1H, ^{13}C$ -COSY spectra of 1 led to the unambiguous assignments of C-1 through C-3 nmr signals (Table 1), and the chemical shift of C-1 (δ 83.5) clearly suggested the presence of an OCH_3 , analogous to compounds such as ranaconitine (3).⁸ Attention was then focused on the placement of the four OH groups and an anisoyl ester on the diterpenoid skeleton. Since a doublet at δ 4.22 ($J = 4.8$ Hz) could be attributed to 14β -H, as in many norditerpenoid alkaloids bearing a hydroxyl at C-14,¹ an OH group was assigned to the 14α position. The 14-H signal indeed showed long-ranged $^1H, ^{13}C$ correlations (HMBC spectrum) with C-8, C-9, and C-16. The presence of three quaternary oxygenated carbons in the ^{13}C -nmr spectrum indicated that the

Table 1.
¹H- and ¹³C-Nmr data for hemsleyanidine (1) and isohemsleyanidine (2) ^{a)}

Position	1		2	
	¹³ C	¹ H (Hz)	¹³ C	¹ H (Hz)
1	83.5 d	3.2 m	83.9 d	3.24 m
2	28.0 t	1.40 m 2.20 m	28.6 t	1.4 m 2.2 m
3	36.9 t	1.98 m 2.37 m	35.0 t	1.8 m 2.32 m
4	41.1 s	--	41.1 s	--
5	36.3 d	2.37 m	37.2 d	2.55 m
6	34.4 t	1.98 m 3.25 m	36.8 t	2.4 m 3.1 m
7	83.8 s	--	84.5 s	--
8	73.5 s	--	74.6 s	--
9	77.0 s	--	77.1 s	--
10	44.5 d	2.00 m	46.0 d	2.05 m
11	50.3 s	--	50.9 s	--
12	25.5 t	2.05 m	25.2 t	2.2 m
13	48.3 d	2.70 m	48.0 d	2.84 m
14	78.4 d	4.22 d (4.8)	82.2 d	5.23 d (4.8)
15	42.0 t	2.30 m 2.75 m	43.9 t	2.25 m 2.65 m
16	75.9 d	5.10 br d (9.2)	74.6 d	3.81 br d (8.3)
17	63.6 d	3.25 s	63.8 d	3.22 s
18	78.4 t	2.96 d (9.3) 3.60 d (9.1)	79.0 t	2.99 (9.2) 3.69 d (9.2)
19	55.3 t	2.00 hidden 2.50 hidden	55.8 t	1.8 hidden 2.55 hidden
NCH ₂ CH ₃	49.0 t	2.4 hidden	49.5 t	2.4 hidden
NCH ₂ CH ₃	13.3 q	1.11 t (7.0)	13.8 q	1.07 t (7.2)
1'	56.3 q	3.27 s	57.0 q	3.27 s
18'	59.4 q	3.31 s	60.0 q	3.36 s
C=O	166.5 s	--	168.3 s	--
1"	122.3 s	--	122.2 s	--
2", 6"	131.7 d	8.01	132.0 d	7.93
3", 5"	113.6 d	6.88	114.3 d	6.91
4"	163.4 s	--	164.1 s	--
4"-OCH ₃	55.3 q	3.82 s	55.8 q	3.81 s

^{a)} Data were recorded on a Bruker ARX-300 spectrometer at 300 MHz for ¹H and 75 MHz for ¹³C. Samples were dissolved in CDCl₃ with TMS as internal standard. Assignments were aided by the interpretation of 2D experiments, including ¹H,¹H-COSY, ¹H,¹³C-COSY and HMBC methods. Some assignments were further confirmed by selective INEPT, COLOC and nOe data.

remaining OH functions are tertiary OH groups. They were then assigned to C-7 (δ 83.8, s), C-8 (δ 73.5, s), and C-9 (δ 77.0, s) on the basis of the following reasons. First, the carbon shift values for the carbons concerned were comparable to those of the 7,8,9-trihydroxyl compounds such as ranaconitine (3) (C-7 δ 85.7; C-8 δ 77.9; C-9 δ 78.4).⁸ Second, other possible substitutions at C-5 and C-10 could be ruled out because C-11 resonated at δ 50.3, which would have otherwise shown a downfield shift due to the β -effect, such as in the case of 7,8-demethylenedeltamine.⁹ Third, another possible location for hydroxyl substitution, C-13, could also be excluded because the ^{13}C shift for C-12 was found at δ 25.5, which would have been shifted to around δ 35 if 13-OH was present (such as in the case of crassicausine and crassicautine).² The methylene carbon signals resonating between δ 34 and 42 were already assigned to C-3, C-6 and C-15 through interpretation of the ^1H , ^1H -COSY and ^1H , ^{13}C -COSY data, as well as by comparison with the reported data of ranaconitine (3)⁸ and tatsinine (6).¹⁰ Lastly, the anisoyl ester was designated to the C-16 by the aid of a selective INEPT experiment. Thus, when the 14-H (δ 4.22) was selectively pulsed, responses of the signals at δ 73.5 (C-8), 77.0 (C-9), and 75.9 were observed. The last signal (a doublet) was therefore ascribed to C-16, which is three bonds away from the H-14. The assignment of the 16-H [δ 5.10 (*br d*, $J = 9.2$ Hz)] was then made possible by an ^1H , ^{13}C -COSY experiment. The configuration of the 16-OAs group was subsequently determined on the basis of nOe results. Thus, when the signal at δ 5.10 (16-H) was irradiated, signal at δ 3.25 (17-H) was enhanced (assignments for these chemical shifts had been confirmed by the ^1H , ^1H -COSY and ^1H , ^{13}C -COSY results). Examination of a Dreiding molecular model indicated that the ring-D may adopt either a *boat* or a *chair* conformation, but only the *boat* conformer would be anticipated to display nOe between 16 α -H and 17-H. The 16-OAs group was thus β -oriented. In order to further vindicate the above deduction, 1 was acetylated with acetyl anhydride in pyridine at room temperature to produce a mixture of 14-acetylhemsleyanidine (4) and the 14-anisoyl-16-acetyl derivative (5) in 1:1 ratio. When this mixture was subjected to an nOe experiment by irradiating the 14 α -OAc (δ 2.1), the signal for 2'/6'-H (δ 7.90, d) was enhanced, and vice versa. Similarly, irradiation of the 3'/5'-H (δ 6.90, d) led to enhancements of the 14 α -OAc, 2'/6'-H, as well as the 4'-OMe (δ 3.85). In addition, it was noted that the migration between the 1,3-diester groups can occur only between 14 α and 16 β positions, presumably through the formation of a cyclic intermediate.

The structure of hemsleyanidine was thus deduced as depicted in 1. It is the first example of lycoctonine-type norditerpenoid alkaloid bearing a 16-anisoyl moiety. Assignments of ^1H - and ^{13}C -nmr data were made by careful analysis of the spectra, including ^1H - ^1H COSY, ^1H , ^{13}C -COSY, HMBC, selective INEPT, and nOe results. The assignments were also compared to the reported values for similar structures such as ranaconitine (3)⁸ and tatsinine (6).¹⁰

Isohemsleyanidine (2), $[\alpha]_D +14.6^\circ$ (CHCl_3 , c 1.0), was isolated as an amorphous powder. Its molecular formula ($\text{C}_{31}\text{H}_{43}\text{NO}_9$) was derived from CI-ms (m/z 574, $[\text{M} + 1]^+$) and the nmr data, indicating 2 being an isomer of 1. Consistent with the ^1H - and ^{13}C -nmr spectra of 1, those of 2 revealed the presence of two methoxyl (δ_{H} 3.27, 3.36; δ_{C} 57.0, 60.0), an anisoyl [δ_{H} 3.81 (3H, s), 6.91, 7.93 (each 2H, AA'BB' system); δ_{C} see Table 1], and an *N*-ethyl [δ_{H} 1.07 (3H, t, $J = 7.2$ Hz); δ_{C} 13.8 q, 49.5 t] groups. In addition to these signals, the ^{13}C -nmr spectrum of 2 exhibited 19 carbon signals, quite similar to those of hemsleyanidine (1) (Table 1). Examination of the ^1H -nmr spectra of these two compounds revealed that the signal at δ 4.22 (*d*, $J = 4.8$ Hz) in 1 disappeared in 2. Instead, a doublet at δ 5.23 ($J = 4.8$ Hz) replaced the H-16 signal (δ 5.1, *br d*, $J = 9.2$ Hz). In addition, the signal at δ 5.23 clearly displayed ^1H , ^{13}C long-ranged correlations (HMBC spectrum) with C-8, C-9, and C-16, indicating that it belonged to 14 β -H. The observation of this downfield shift of 14 β -H (compared to 1) suggested that the 14 α -OH was esterified in 2.

The structure of isohemsleyanidine (2) was thus derived to be the 14 α -OAc, 16 β -OH-isomer of hemsleyanidine. The nmr spectral data (Table 1) were assigned by ^1H , ^1H -COSY, ^1H , ^{13}C -COSY, and HMBC studies.

Hydrolysis of either hemsleyanidine (1) or isohemsleyanidine (2) in methanolic NaOH produced the same alkaline product, hemsleyanidine (7). Acetylation of the alkaline 7 with acetyl anhydride in pyridine afforded 14,16-diacetyl-hemsleyanidine (8) and 16-acetyl-hemsleyanidine (9). The ^{13}C -nmr spectral data of 7, 8 and 9 are shown in Table 2.

EXPERIMENTAL

PLANT MATERIAL.-- *A. hemsleyanum* var. *circinatum* roots were collected in September 1991 in Emei Mountain, Sichuan, China. The plant was identified by Prof. W. T. Wang (Institute of Botany, Chinese Academy of Sciences, Beijing), and voucher specimens have been deposited in the herbarium of the School of Pharmacy, West China University of Medical Sciences.

EXTRACTION AND SEPARATION.-- Powdered roots (2 kg) were percolated with 0.015% HCl (20 litres) at room temperature for three days. A polyvinyl sulphonic ion resin (H form, cross linking 1x3, Nan Kei University, China)(200 g) was used to treat the percolates. After exchange, the resin was washed repeatedly on a suction filter with deionized water, spreaded out and air dried. The resin was then well mixed with 10% ammonium water (total amount 760 ml) and extracted in a specially designed extractor¹¹ with ether under reflux for 6 h. Crude total alkaloids (9.5 g) were obtained as a white powder. The total alkaloid fraction (9 g) was subsequently chromatographed on silica gel and eluted with cyclohexane-ethyl acetate-diethylamine (8:1:1) to afford fractions A (2.1 g), B (1.1 g), C (0.7 g), D (1.0 g) and E (3.2 g).

ISOLATION OF TALATIZAMINE.-- Fraction A (1.3 g) was chromatographed on silica gel and eluted with

Table 2 ^{13}C -Nmr data for 7, 8 and 9 ^{a)}

Position	7	8	9
1	83.8 d	83.5 d	83.5 d
2	25.7 t	25.8 t	26.0 t
3	34.2 t	34.6 t	34.5 t
4	41.2 s	41.0 s	41.1 s
5	36.9 d	37.1 d	36.3 d
6	35.3 t	37.3 t	36.3 t
7	84.6 s	84.2 s	83.9 s
8	73.4 s	73.5 s	73.5 s
9	76.3 s	76.4 s	75.9 s
10	44.9 d	45.0 d	44.5 d
11	50.4 s	50.4 s	50.4 s
12	28.2 t	28.3 t	28.1 t
13	48.5 d	48.3 d	48.4 d
14	79.3 d	82.9 d	79.6 d
15	43.5 t	41.9 t	41.9 t
16	75.4 d	75.5 d	74.0 d
17	63.9 d	63.2 d	63.9 d
18	78.5 t	78.7 t	78.5 t
19	55.3 t	55.3 t	55.6 t
NCH_2CH_3	49.2 t	49.2 t	49.2 t
NCH_2CH_3	13.7 q	13.6 q	13.4 q
1'	55.6 q	56.5 q	56.4 q
18'	59.6 q	59.6 q	59.6 q
$\text{O}=\text{CCH}_3$	--	170.0 s	171.3 s
	--	173.0 s	--
$\text{O}=\text{CCH}_3$	--	21.1 q	21.4 q
	--	21.3 q	--

^{a)} Data were recorded on a Bruker AC-200 spectrometer. Samples were dissolved in CDCl_3 with TMS as internal standard.

CHCl_3 -MeOH (99:1) to give a white amorphous powder (25 mg) showing one spot on tlc. The compound was identified as talatizamine by comparison with the published spectroscopic data.⁶

ISOLATION OF HEMSLEYANIDINE (1).-- Fr. D (0.9 g) was chromatographed on a column of silica gel and eluted successively with CHCl_3 containing increasing amounts of MeOH (4% - 100%) to afford a white powder hemsleyanidine (1) (150 mg). Compound 1 showed a single spot on tlc. ^1H -Nmr (300 MHz, CDCl_3) and ^{13}C -nmr (75 MHz): see Table 1. CI-ms: m/z 574 $[\text{M} + 1]^+$, 556 $[\text{M} - \text{OH}]^+$, 404.

ACETYLATION OF 1.-- To 20 mg of hemsleyanidine (1) were added 1 ml of pyridine and 0.5 ml of acetyl anhydride. The solution was allowed to stand at room temperature overnight. Removal of the solvent under reduced pressure gave a residue. ¹H-Nmr spectrum (400 MHz, recorded on a Jeol EX-400 spectrometer in CDCl₃) showed that it was a mixture of the 14 α -acetyl,16 β -anisoysl derivative (14-acetyl isohemsleyanidine, 4) [δ 5.06 (*d*, *J* = 4.2 Hz, 14 β -H), 5.53 (*dd*, *J* = 6.2, 3.6 Hz, 16 α -H)] and the 14 α -anisoysl,16 β -acetyl derivative (5) [δ 5.44 (*d*, *J* = 5.1 Hz, 14 β -H), 5.24 (*dd*, *J* = 6.3, 3.3 Hz, 16 α -H)]. Other signals of the mixture included δ 2.07 (6H, *s*, 2 x OAc), 3.27, 3.33 (each 3H, *s*, 2 x OCH₃), 3.84 (3H, *s*, aromatic OCH₃), 6.90, 7.92 (each 2H, AA'BB' system, aromatic protons). The proportions of 4:5 were determined to be approx. 1:1 based on the integration of the 14 β -H signals. The 1D nOe experiments of the mixture revealed nOe relationships between the 3'/5'-H and 14 α -OAc; the 14 α -OAc and 2'/6'-H (or the 4'-OMe), and vice versa.

ISOLATION OF ISOHEMSLEYANIDINE (2).-- Fractions E (1.5 g) was repeatedly chromatographed on a silica gel column and eluted with CHCl₃-MeOH (95:5) to afford isohemsleyanidine (2) (450 mg), which appeared as an amorphous powder showing a single spot on tlc. ¹H-Nmr (300 MHz, CDCl₃) and ¹³C-nmr (75 MHz): see Table 1. CI-ms: *m/z* 574 [*M* + 1]⁺, 556 [*M* - OH]⁺.

HYDROLYSIS OF 1.-- To 10 mg of hemsleyanidine (1) was added 1 ml of 5% methanolic sodium hydroxide. The solution was allowed to stand at room temperature overnight. Removal of the solvent under reduced pressure provided a residue, to which was added 10 ml of water and extracted with CHCl₃ (10 ml x 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to give an amorphous powder (hemsleyanidine 7) showing a single spot on tlc. ¹H-Nmr (200 MHz, CDCl₃) of 7: δ 1.03 (3H, *t*, *J* = 6.7 Hz, NCH₂CH₃), 2.97, 3.63 (each 1H, AB system, *J* = 9.2 Hz, 18-CH₂), 3.19 (1H, *s*, 17-H), 3.24, 3.32 (each 3H, *s*, 2 x OCH₃), 3.74 (1H, *br s*, 16 α -H), 4.20 (1H, *d*, *J* = 4.6 Hz, 14 β -H), 4.20 (1H, D₂O exchangeable, OH). ¹³C-Nmr (50 MHz): see Table 2.

HYDROLYSIS OF 2.-- Isohemsleyanidine (2, 12 mg) was treated in the same manner as described for the hydrolysis of 1 to afford a white glue. The product was shown to be identical to 7 by tlc analysis.

ACETYLATION OF 7.-- To 110 mg of 7 was added a mixed solution containing acetic anhydride and pyridine (3 ml each). The solution was allowed to stand at room temperature overnight. Removal of the solvent under reduced pressure provided a residue, which was alkalized to pH 9 with NH₄OH, and extracted with CHCl₃ (10 ml x 3). The organic layers were dried over anhydrous Na₂SO₄ and concentrated to afford a white residue showing two spots on tlc. The residue was subsequently chromatographed on a chromatotron over silica gel G developed with CHCl₃-MeOH (99:1 and then 98:2) to afford 14,16-diacetylhemsleyanidine (8, 45 mg) and 16-acetylhemsleyanidine (9, 40 mg).

Compound (8) was obtained as an amorphous powder; ¹H-nmr (200 MHz, CDCl₃): δ 1.03 (3H, *t*, *J* = 7.2 Hz, NCH₂CH₃), 2.01, 2.18 (each 3H, *s*, 2 x OAc), 3.20 (1H, *s*, 17-H), 3.23, 3.32 (each 1H, *s*, 2 x OCH₃), 2.95, 3.65 (each 1H, AB system, *J* = 9.1 Hz, 18-CH₂), 4.12, 4.35 (each 1H, D₂O exchangeable, OH), 4.90 (1H, *br d*, *J* = 9.6 Hz, 16 α -H), 5.00 (1H, *d*, *J* = 5.3 Hz, 14 β -H). ¹³C-Nmr (50 MHz): see Table 2. EI-ms: *m/z* 523 [*M*]⁺, 492 [*M* - OCH₃]⁺.

Compound (9) was obtained as an amorphous powder; ^1H -nmr (200 MHz, CDCl_3): δ 1.03 (3H, *t*, $J = 7.1$ Hz, NCH_2CH_3), 2.12 (3H, *s*, OAc), 3.23, 3.32 (each 3H, *s*, $2 \times \text{OCH}_3$), 2.95, 3.63 (each 1H, AB system, $J = 12.2$ Hz, 18- CH_2), 4.10 (1H, *s*, D_2O exchangeable, OH), 4.89 (1H, *br d*, $J = 9.7$ Hz, 16 α -H). ^{13}C -Nmr (50 MHz): see Table 2. EI-*ms*: *m/z* 481 [M^+], 450 [$\text{M} - \text{OCH}_3$] $^+$.

ACKNOWLEDGEMENT

The authors thank Prof. W.T. Wang (Institute of Botany, Chinese Academy of Sciences, Beijing) for authenticating the plant materials, and we acknowledge the skillful assistance of Ms. Eunice Y.L. Chan (HKUST) for acquiring 2D-nmr data.

REFERENCES

1. S.W. Pelletier, N.V. Mody, B.S. Joshi, and L.C. Schramm, "Alkaloids: Chemical and Biological Perspectives", Vol. 2, ed. by S.W. Pelletier, Wiley, New York, 1984, pp. 206-642; S.W. Pelletier and B.S. Joshi, "Alkaloids: Chemical and Biological Perspectives", Vol. 7, ed. by S.W. Pelletier, Wiley, New York, 1991, pp. 297-564.
2. F.P. Wang and S.W. Pelletier, *J. Nat. Prod.*, 1987, **50**, 55.
3. F.P. Wang and S.W. Pelletier, *Acta Botanica Sinica*, 1990, **32**, 733.
4. H.Y. Pu and F.P. Wang, *Acta Pharm. Sinica*, 1994, **29**, 689.
5. H.Y. Pu and F.P. Wang, *Chinese Chem. Lett.*, 1994, **5**, 939.
6. S.W. Pelletier, N.V. Mody, B.S. Joshi, and L.C. Schramm, "Alkaloids: Chemical and Biological Perspectives", Vol. 2, ed. by S.W. Pelletier, Wiley, New York, 1984, p. 451.
7. S.Y. Chen, *Acta Chimica Sinica*, 1979, **37**, 15.
8. S.W. Pelletier, N.V. Mody, and A.P. Venkov, *Tetrahedron Lett.*, 1978, 5045.
9. S.W. Pelletier, H.K. Desai, P. Kulanthaivel, and B.S. Joshi, *Heterocycles*, 1987, **26**, 2835.
10. J.A. Glinski, B.S. Joshi, S.Y. Chen, and S.W. Pelletier, *Tetrahedron Lett.*, 1984, **25**, 1211.
11. Q.C. Fang and Z.M. Hou, *Acta Pharm. Sinica*, 1966, **13**, 577.

Received, 19th February, 1996